SiteMap

Fast, accurate, and practical binding site identification

Combining a novel algorithm for rapid binding site identification and evaluation with easy-to-use property visualization tools, SiteMap provides researchers with an efficient means to find and better exploit the characteristics of ligand binding sites.

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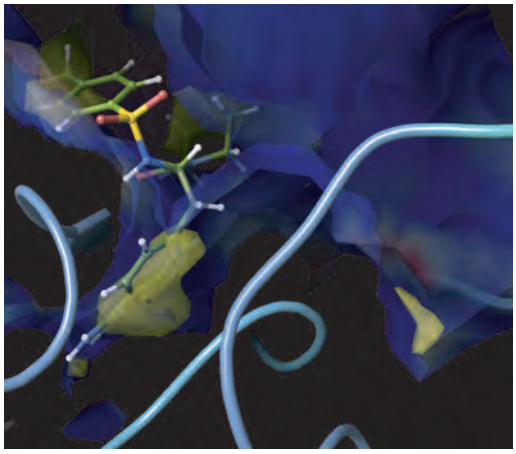
The Importance of Understanding Protein Sites

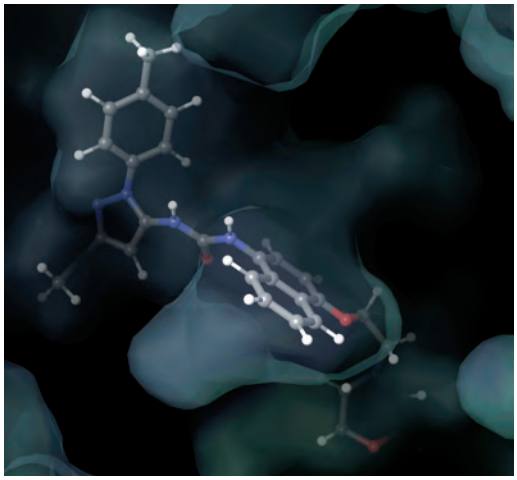


The protein surface for 1ett and the active site hydrophobic regions calculated by SiteMap are shown here. In tests across 274 protein structures taken from the PDB, SiteMap correctly identifies 94% of all ligand-binding sites. Furthermore, for sub-micromolar binding sites, SiteMap's accuracy improves to 98%.

Understanding the structure and exploiting the function of protein active sites is a cornerstone of drug design. Doing so requires chemists to know the location of these sites, yet at the outset of many drug design projects the location of a binding site for protein-ligand or protein-protein interactions remains unknown. Additionally, it is equally important to identify the locations of any potential allosteric binding sites.

SiteMap's proven algorithm for binding site identification and evaluation can help researchers to locate binding sites with a high degree of confidence and to predict the drugability of those sites. Beyond lead discovery, SiteMap assists in lead optimization by providing insight into ligand-receptor interactions so as to suggest effective strategies to modify lead compounds in order to enhance receptor complementarity.

SiteMap: Maximizing Returns in Structure-Based Drug Design

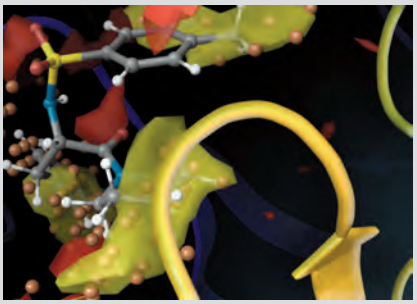


The binding site for 1kv2, shown here, features a buried hydrophobic region that SiteMap is tuned to recognize.

SiteMap is Schrödinger's program for identifying, evaluating, and visualizing ligand binding sites. Designed to address common issues in the lead discovery and optimization phases of drug discovery projects, SiteMap's features include:

- **Rapid site identification and ranking:** SiteMap can treat entire proteins to locate binding sites whose size, functionality, and extent of solvent exposure meet user specifications. SiteScore, the scoring function used to assess a site's propensity for ligand binding, accurately ranks possible binding sites to eliminate those not likely to be pharmaceutically relevant.
- **Integration with Glide:** SiteMap fits perfectly into the Schrödinger structure-based drug design workflow. Sites identified by SiteMap can easily be used to set up Glide grids for virtual screening experiments.
- **Site visualization tools:** SiteMap can display the protein surface and depict three-dimensional regions within the binding site suitable for occupancy by hydrophobic groups, H-bond donors, acceptors, or metal-binding functionality. Distinguishing the different binding site sub-regions allows for ready assessment of a ligand's complementarity.
- **Tools for exploiting targets of opportunity:** Active site maps show where modifications to a ligand structure could promote binding.
- **Easy-to-use interface:** SiteMap is integrated with Maestro, the common graphical user interface for all Schrödinger products. Key results of the SiteMap calculation are automatically incorporated into the Maestro project table.
- **Cross-platform support:** SiteMap offers excellent performance on both Linux and SGI platforms.

Performance-Driven Technology



In 1ett, SiteMap identifies the binding site's hydrophobic regions (shown in yellow), H-bond acceptor regions (shown in red), and other regions not displayed here. SiteMap uses the following terms to characterize protein-ligand binding sites:

SiteScore: Overall binding score
Size: Number of "site points" contained within site
Exposure: Measure of exposure to solvent
Enclosure: Degree to which protein surface encloses site
Contact: Relative tightness of van der Waals contact with protein
Phob: Relative degree of site's hydrophobicity
Phil: Relative degree of site's hydrophilicity
Balance: Ratio of hydrophobic to hydrophilic character
Don/Acc: Relative donor versus acceptor H-bonding opportunities

SiteMap features innovative methodologies throughout the computational workflow:

- **Finding sites:** SiteMap identifies potential ligand binding sites by linking together "site points" that are suitably close to the protein surface and sufficiently well sheltered from the solvent. Given that similar terms dominate the site scoring function, this approach ensures that the search focuses on regions of the protein most likely to produce tight protein-ligand or protein-protein binding. Subsites are merged into larger sites when they are sufficiently close and could be bridged in solvent-exposed regions by ligand atoms.

- **Visualizing sites:** SiteMap uses an enhanced definition of hydrophobicity akin to that employed by the Glide XP scoring function, and favors hydrophobic regions that are sheltered from the solvent. To provide better visual guidance, SiteMap highlights regions within the binding site suitable for occupancy by hydrophobic groups or by ligand hydrogen-bond donors, acceptors, or metal-binding functionality.

- **Evaluating sites:** SiteMap evaluates sites using a series of properties that are automatically incorporated into the project table, where they can be analyzed, saved as a spreadsheet, or stored for future reference. The key term, SiteScore, has been parametrized based upon known binding sites of co-crystallized complexes. SiteScore and other properties are reported in relative values compared to the average computed across a large number of tight-binding ($\leq 1\ \mu M$) sites, making it straightforward to rank-order potential binding sites.

Identifying Sites in Proteins

Performance in Locating the Primary Binding Site in Proteins

Comparison	274 Proteins %	157 Tight Binders %
No close site found	2.6	0.0
Largest site is correct site	84.7	89.2
Best-scoring site is correct site	93.8	98.1
Largest or best-scoring site is correct site	94.9	98.7

In validation tests SiteMap has proven capable of identifying ligand-binding sites with considerable accuracy. Across tests of 274 diverse proteins taken from the PDB, SiteMap locates the correct binding site for 94% of all proteins. SiteMap's performance is even better when only the stronger binding complexes are considered – among the 157 proteins in the test set with measured ligand binding affinities less than one micromolar, SiteMap locates the correct binding site 98% of the time.

In addition to rank-ordering binding sites within a protein, researchers may opt to select a SiteScore threshold to distinguish between drug-binding and non-drug-binding sites. When using such a protocol in validation studies, SiteMap correctly distinguishes 86% of binding sites for the full test set, and 90% of sub-micromolar sites.

Evaluation Copies

To request an evaluation copy of SiteMap, please contact info@schrodinger.com. Our staff of support scientists will be happy to assist you in giving SiteMap a thorough trial.

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A Coordinated Family of Products

SiteMap is an ideal complement to other Schrödinger products for lead discovery and lead optimization, including:

- **Glide:** High-throughput ligand-receptor docking for fast library screening
- **Prime:** Ligand-receptor binding free energies for lead optimization
- **QSite:** A high-performance QM/MM program

All Schrödinger products are seamlessly integrated through the Maestro graphical interface.

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